

HEALTH EFFECTS DIVISION  
SCIENTIFIC DATA REVIEWS  
EPA SERIES 331

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DATA EVALUATION REPORT

**STUDY TYPE:** Combined Chronic/oncogenicity - Rats [83-5(a)]  
**DP BARCODES:** D188679 **SUBMISSION:** S436173  
D189620  
**P.C. CODE:** 069149 **CASWELL NO.:** 331A  
**MRID NO.:** 419651-01  
**TEST MATERIAL:** BARDAC 2280  
**SYNONYMS:** Didecyldimethylammoniumchloride  
**STUDY NUMBER:** 53-566  
**SPONSOR:** Lonza, Inc., 17-17 Route 208, Fair Lawn, NJ  
**TESTING FACILITY:** Bushy Run Research Center, R.D. #4, Mellon Road, Export, PA  
**TITLE OF REPORT:** Chronic dietary toxicity/oncogenicity study with decyldimethylammoniumchloride  
**AUTHOR:** M.W. Gill, J.S. Chun and C.L. Wagner  
**REPORT ISSUED:** 27 June 1991

**CONCLUSIONS:** Male and female rats were fed diets containing BARDAC 2280 at 0, 300, 750 or 1500 ppm (mg/kg/day equivalents: 0, 13, 32, or 64 for males and 0, 16, 41, or 83 for females) for two years. High-dose animals showed significant, but slight (< 10%) decreases in mean body weight during the study. Treatment related effects consisted of increased incidence of sinusoidal blood, hemosiderosis and histiocytosis in the mesenteric lymph nodes of high dose animals. The incidence of neoplastic lesions in treated animals was comparable to controls. BARDAC 2280 was not carcinogenic in male or female rats.

	<u>NOEL</u>	<u>LOEL</u>
Males & Females	750 ppm (MDT)	1500 ppm (HDT)

The LOEL is based on increased incidence on nonneoplastic lesions in the mesenteric lymph nodes (sinusoidal blood, hemosiderosis and histiocytosis).

**CORE CLASSIFICATION:** Minimum. This study satisfies guideline requirements [83-5(a)] for a combined chronic toxicity/oncogenicity study in rats and is acceptable for regulatory purposes.

## A. MATERIALS:

1. Test compound: BARDAC 2280 Description: viscous, honey-colored liquid Batch #: B-1889 Purity: 80.8% [a.i.] Contaminants: not given

2. Test animals: Species: Rat Strain: Sprague-Dawley CD Age: 8 weeks Weight (g): 237.7 - 295.9 (males), 154.8 - 199.7 (females) Source: Charles River Breeding Laboratories, Inc., Portage, MI. Housing: Individually in suspended cages Feed: Purina Certified Rodent Chow #5002 Water: Tap water, *ad libitum* Environment: Temperature, 66 - 75 °F; Humidity, 40 - 70%; Light cycle, 12 hr light/12 hr dark; Air changes, at least eight per hour.

## B. METHODS

1. Animal Assignments: Animals were assigned randomly to main study test groups as shown in Table 1.

Table 1: Animal Assignment to Study Groups

Test Group	Dosage <sup>a</sup> (ppm)	Animals/Group	
		Male	Female
Control 1 (CON1)	0	60	60
Low (LDT)	300	60	60
Mid (MDT)	750	60	60
High (HDT)	1500	60	60
Control 2 (CON2)	0	60	60

<sup>a</sup> Dosage adjusted for percent purity of active ingredient

2. Justification for Dose Selection: Doses for this study were selected based on dose range-findings studies (BBRC Report Numbers 51-506 and 51-560). The 90-day study (51-506) was submitted and reviewed by the Agency (MRID No. 409663-02).

3. Diet Preparation: A weighed amount test compound was mixed with basal diet to form a concentrated premix, which was thoroughly mixed to ensure evaporation of ethanol. Diets were prepared by serial dilution of the premix or higher diet concentrations.

4. Statistical Evaluations: Parametric data were initially evaluated for homogeneity of variances using Levene's test. Homogeneous data were then analyzed using a one-way analysis of variance (ANOVA) and pooled variance t-tests. Data found to be heterogeneous were evaluated using ANOVA for unequal variances followed by separate variance t-tests. Parametric

data were evaluated using either the Kruskal-Wallis test or the Mann-Whitney-modified Wilcoxon rank sum test. Frequency data were evaluated using the Fisher's exact test.

This study contained two control groups. For statistical purposes, each control group was treated separately.

C. REGULATORY COMPLIANCE

1. Quality assurance was documented by signed and dated GLP and quality assurance statements.
2. The sponsor applied the criteria of 40 CFR 158.34 for flagging studies for potential adverse effects to the results of this study. This study neither meets nor exceeds any of the applicable criteria.
3. A statement of "no confidentiality claims" was provided.

D. RESULTS

1. Analytical Chemistry: The prepared diets were analyzed for stability, homogeneity and concentration. The 300 and 1500 ppm test diets were stable for at least 21 days at room temperature and were 99.9 to 108% and 97.6 to 105.8% of nominal, respectively. For determination of homogeneity, samples were taken from the top, middle and bottom of the mixing bowl. The 300, 750 and 1500 ppm diets were within 98.3 to 107.0%, 102.1 to 106.1% and 95.1 to 104.3% of nominal, respectively. Verification of concentration was performed weekly for the first month and at monthly intervals, thereafter. Throughout the study, the concentrations of test compound were within 91.6 to 109.2% of nominal.

2. Observations: Animals were inspected twice daily for signs of toxicity, mortality and moribundity. Detailed clinical examinations, including palpable masses, were performed weekly.

a. Clinical observations: No clinical signs attributable to treatment were observed during the study. The incidence of palpable masses in males and females was comparable among all of the dose groups.

b. Mortality: A summary of animal fate data is presented in Table 2. The percent mortalities (excluding accidental deaths) and mean survival times were comparable among all of the study groups.

4. Body Weight and Body Weight Gain: Body weights were measured at the start of the study, at weekly intervals through Week 14, and every other week, thereafter.

Table 2: Summary of Mortality (Data summarized from Table 1 of study)

Fate of animals	Sex	Dietary Concentration (ppm)				
		0 <sup>a</sup>	300	750	1500	0 <sup>b</sup>
Found dead	♂	14	15	21	13	13
	♀	8	11	8	10	9
Moribund sacrifice	♂	7	18	12	13	15
	♀	22	13	12	12	21
Percent Mortality <sup>c</sup>	♂	35	55	43	47	47
	♀	50	40	33	37	50
Accidental deaths	♂	2	0	0	1	0
	♀	0	0	1	0	0
Terminal sacrifice	♂	37	27	27	33	32
	♀	30	36	39	38	30
Mean survival time (days)	♂	692	658	673	677	599
	♀	675	684	675	699	669

<sup>a</sup> Control 1<sup>b</sup> Control 2<sup>c</sup> Excludes accidental deaths

a. Body weights: Mean body weights for selected time intervals are summarized in Table 3. Consistent decreases in body weights were limited to animals in the high-dose groups. The mean body weights of high-dose males were lower than either control for the entire study. Statistically significant changes from both controls were noted from Weeks 4 to 8, Week 10, and Weeks 18 to 20; values were significantly lower than the first control on Weeks 22, 24, and 88. The mean body weights of high-dose females were lower than either control for the entire study. Statistically significant changes from both controls were limited to Weeks 5, 6, and 7. Significant differences from the first, but not second, control were noted on Weeks 4, 11, 13 to 50, 54, and 58 to 104. Overall, the changes in mean body weights for the high-dose animals were considered slight. For males, body weights were 0.4 to 6.5% lower than the first control and 2.0 to 4.1% lower than the second control. For most of the study, female body weights were 1.2 to 7.3% lower than the first control and 0.6 to 6.0% lower than the second control. Body weights for high-dose females at Week 104 were 11.4% lower than values for the first control. Other significant findings were present in the low- and mid-dose groups, but were sporadic in nature and not considered treatment-related.

Table 3: Mean Body Weights (Data summarized from Tables 5 and 7 of study)

Week	Mean Body Weights, g				
	0 ppm (CON1)	300 ppm	750 ppm	1500 ppm	0 ppm (CON2)
<b>Males</b>					
0	269	267 (-0.6, 0.5) <sup>a</sup>	268 (0.5, 1.0)	266 (-0.4, 0.1)	266
1	316	315 (-0.5, 0.1)	315 (0.2, 0.3)	308 (-2.1, -2.0)	314
2	352	352 (0.2, 0.2)	352 (0.1, 0.2)	344 (-2.3, -2.2)	352
4	405	405 (0.0, 0.4)	406 (0.3, 0.7)	392 <sup>ad</sup> (-3.2, -2.9)	403
8	486	482 (-0.8, 0.1)	484 (0.4, 0.5)	467 <sup>ad</sup> (-3.0, -2.9)	481
12	531	526 (-0.8, 0.5)	530 (0.6, 1.1)	509 (-3.2, -2.8)	524
16	561	561 (-0.1, 0.8)	560 (-0.2, 0.5)	540 (-3.8, -3.1)	557
24	603	597 (-0.9, 1.6)	596 (-0.1, 1.5)	572 <sup>c</sup> (-4.3, -2.7)	587
32	630	627 (-0.5, 0.3)	630 (0.5, 0.8)	603 (-3.8, -3.6)	625
40	664	663 (-0.1, 0.5)	666 (0.5, 1.1)	640 (-3.4, -2.9)	659
56	710	705 (-0.7, -0.1)	710 (0.7, 0.6)	680 (-3.6, -3.8)	706
72	738	729 (-1.2, 0.2)	733 (0.6, 0.8)	702 (-3.7, -3.5)	727
88	763	740 (-2.9, 2.6)	736 (-0.6, 2.0)	692 <sup>c</sup> (-6.5, -4.1)	722
104	701	681 (-2.8, -1.3)	699 (2.6, 1.3)	677 (-0.6, -1.9)	690
.....					
<b>Females</b>					
0	179	179 (0.2, 1.5)	177 (-0.8, 0.7)	177 (-1.2, 0.3)	176
1	198	199 (0.5, 0.6)	199 (0.0, 0.6)	197 (-1.2, -0.6)	198
2	216	216 (0.0, 1.1)	216 (-0.2, 0.9)	212 (-1.9, -0.8)	214
4	243	244 (0.3, 1.5)	243 (-0.4, 1.2)	235 <sup>b</sup> (-3.5, -2.0)	240
8	274	274 (0.2, 1.1)	274 (-0.3, 0.8)	265 (-3.4, -2.2)	271
12	290	291 (0.3, 1.6)	290 (-0.3, 1.2)	280 (-3.9, -2.4)	286
16	307	306 (-0.5, 1.2)	307 (0.5, 1.7)	293 <sup>c</sup> (-4.2, -3.1)	302
24	328	324 (-1.1, 1.1)	329 (1.4, 2.5)	310 <sup>c</sup> (-4.3, -3.3)	321
32	356	348 (-2.3, 1.0)	356 (2.4, 3.4)	334 <sup>c</sup> (-3.9, -2.9)	344
40	384	377 (-2.0, 1.9)	384 (1.8, 3.7)	356 <sup>c</sup> (-5.6, -3.9)	370
56	423	418 (-1.2, 1.9)	429 (2.5, 4.4)	396 (-5.3, -3.5)	411
72	455	453 (-0.5, 3.4)	467 (3.2, 6.7)	425 <sup>b</sup> (-6.2, -3.0)	438
88	499	488 (-2.2, 1.4)	519 <sup>d</sup> (6.2, 7.7)	453 <sup>b</sup> (-7.3, -6.0)	482
104	492	480 (-2.4, 7.2)	501 (4.2, 11.7)	425 (-11.4, -5.1)	448

<sup>a</sup> Values in parentheses represent percent of control (% of CON1, % of CON2)

<sup>b</sup> Significant difference from CON1 ( $p \leq 0.05$ )

<sup>c</sup> Significant difference from CON1 ( $p \leq 0.01$ )

<sup>d</sup> Significant difference from CON2 ( $p \leq 0.05$ )

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b. Body weight gains: Body weight gains for selected intervals are summarized in Table 4. For high-dose males, body weight gains were lower than control values for the entire study. Differences were statistically significant from both controls for Weeks 0 through 12 and for Week 0 to 18, 20 and 22; significant differences from the first control only were noted for Weeks 0 to 24. Body weight gains for high-dose females were significantly lower than both controls for Weeks 0 to 7, 11, 12, 14, 16, and 78; significant differences from the first control were noted for Weeks 0 to 13, 18, 22, 26 through 76, and 80 through 104. Weight gains were significantly lower than the second control for Weeks 0 to 3. Occasional significant differences from one, but not both, controls were noted in the mid-dose males and females.

Table 4: Mean Body Weight Gains (g) (Data summarized from Tables 6 and 8 of study)

Week	0 ppm (CON1)	300 ppm	750 ppm	1500 ppm	0 ppm (CON2)
<b>Males</b>					
0 - 1	47.6	47.7	47.0	42.0 <sup>bd</sup>	48.6
0 - 2	83.0	85.2	84.0	78.0 <sup>ad</sup>	85.8
0 - 4	136.2	137.6	137.6	125.6 <sup>bd</sup>	137.4
0 - 8	217.0	215.0	215.5	201.3 <sup>bd</sup>	215.5
0 - 12	261.9	259.2	261.1	243.1 <sup>bc</sup>	257.9
0 - 16	292.7	294.1	291.3	273.7	291.0
0 - 24	333.9	330.0	327.8	305.5 <sup>b</sup>	321.5
0 - 32	361.3	359.9	361.5	335.8	359.2
0 - 40	395.0	395.8	398.0	373.9	393.7
0 - 56	442.1	437.9	441.8	413.9	440.6
0 - 72	469.4	460.9	465.1	435.7	461.7
0 - 88	494.3	472.7	468.6	426.7	455.2
0 - 104	432.5	414.6	434.7 <sup>c</sup>	413.5	425.3
.....					
<b>Females</b>					
0 - 1	19.5	20.2	21.7	20.1	21.7
0 - 2	37.4	37.2	38.3	35.3	37.7
0 - 4	64.5	65.1	65.7	58.6 <sup>bd</sup>	64.1
0 - 8	95.4	95.6	96.4	88.6	95.3
0 - 12	111.5	112.1	112.6	103.0 <sup>ac</sup>	110.3
0 - 16	128.7	126.9	129.8	116.2 <sup>bc</sup>	126.0
0 - 24	149.2	145.4	151.5	133.5 <sup>bc</sup>	144.6
0 - 32	177.5	169.1	179.0	157.7 <sup>b</sup>	168.3
0 - 40	205.7	197.9	206.4	178.9 <sup>b</sup>	193.8
0 - 56	244.7	239.6	251.4	219.5	234.3
0 - 72	277.1	274.2	290.2	248.3 <sup>a</sup>	262.1
0 - 88	320.8	310.7	341.7	277.3 <sup>a</sup>	306.4
0 - 104	314.3	303.6	323.9 <sup>c</sup>	251.6 <sup>a</sup>	274.0

<sup>a</sup> Significant difference from CON1 ( $p \leq 0.05$ )

<sup>b</sup> Significant difference from CON1 ( $p \leq 0.01$ )

<sup>c</sup> Significant difference from CON2 ( $p \leq 0.05$ )

<sup>d</sup> Significant difference from CON2 ( $p \leq 0.01$ )

5. Food Consumption: Food consumption was measured at weekly intervals through Week 14 and every other week, thereafter. Statistically significant differences in food consumption were noted in both males and females throughout the study (Table 5, below). The occurrence was, however, sporadic in nature and therefore, did not appear to be a treatment-related effect.

Table 5: Food Consumption (g/animals/day) (Data summarized from Tables 9 and 10 of study)

Week	0 ppm (CON1)	300 ppm	750 ppm	1500 ppm	0 ppm (CON2)
<u>Males</u>					
0 - 1	24.5	24.2 <sup>d</sup>	24.0 <sup>d</sup>	23.2 <sup>bd</sup>	25.5 <sup>a</sup>
3 - 4	26.5	26.5	24.9	24.1 <sup>bc</sup>	25.2 <sup>b</sup>
4 - 5	25.5	26.4 <sup>c</sup>	25.0	23.4 <sup>bc</sup>	25.1
5 - 6	25.8	25.3	24.5 <sup>b</sup>	23.3 <sup>bd</sup>	25.2
6 - 7	25.8	25.0 <sup>a</sup>	24.9 <sup>a</sup>	23.7 <sup>bd</sup>	25.8
7 - 8	26.0	25.1	25.4	24.2 <sup>bd</sup>	26.1
8 - 9	25.0	24.9	25.0	24.1 <sup>ad</sup>	25.3
9 - 10	25.4	25.0	25.0	24.2 <sup>bd</sup>	25.7
10 - 11	25.4	25.3	25.3	24.2 <sup>bd</sup>	25.5
11 - 12	25.8	25.0 <sup>ac</sup>	25.1	24.6 <sup>bd</sup>	26.0
12 - 13	24.9	24.6 <sup>c</sup>	24.6 <sup>c</sup>	24.3 <sup>d</sup>	25.6
15 - 16	26.6	27.0 <sup>d</sup>	26.2	25.2 <sup>b</sup>	25.9
35 - 36	24.8	25.5	25.5	24.4 <sup>c</sup>	25.4
41 - 42	26.2	26.3	26.5	25.1 <sup>ac</sup>	26.1
45 - 46	26.1	26.0	26.6	25.4 <sup>d</sup>	26.8
55 - 56	26.2	25.7	25.6	24.73 <sup>b</sup>	25.1
65 - 66	26.9	26.5	27.0	25.1 <sup>a</sup>	25.8
69 - 70	26.5	25.6	26.1	24.8 <sup>bd</sup>	26.5
87 - 88	25.5	24.1	24.2	22.3 <sup>bc</sup>	24.9
97 - 98	25.1	23.7 <sup>d</sup>	24.3 <sup>d</sup>	24.1 <sup>d</sup>	27.7 <sup>a</sup>
.....					
<u>Females</u>					
0 - 1	17.5	17.4	17.1	15.9 <sup>bd</sup>	17.2
2 - 3	18.1	17.8	18.2	17.2 <sup>bd</sup>	18.3
3 - 4	18.3	18.7	18.4	17.2 <sup>bd</sup>	18.4
4 - 5	18.4	17.9	18.0	17.0 <sup>bd</sup>	18.1
5 - 6	18.0	17.9	17.8	17.1 <sup>bd</sup>	18.3
6 - 7	17.7	16.9 <sup>bd</sup>	17.8	17.1 <sup>ac</sup>	17.8
8 - 9	17.3	17.7	18.1 <sup>ad</sup>	18.2 <sup>ad</sup>	17.2
11 - 12	18.1	17.7	17.6	17.2 <sup>b</sup>	17.2 <sup>b</sup>
12 - 13	17.8	17.2 <sup>a</sup>	17.6	17.0 <sup>b</sup>	17.3 <sup>a</sup>
15 - 16	18.2	17.3 <sup>a</sup>	18.6 <sup>c</sup>	17.2 <sup>a</sup>	17.8
17 - 18	18.6	17.9 <sup>a</sup>	18.6	17.7 <sup>bc</sup>	18.5
25 - 26	19.7	18.9 <sup>a</sup>	19.2	17.7 <sup>bc</sup>	18.8 <sup>a</sup>
27 - 28	19.5	19.3	19.8 <sup>c</sup>	18.6 <sup>a</sup>	18.8
35 - 36	19.2	19.5	19.7 <sup>c</sup>	18.2 <sup>a</sup>	18.8
41 - 42	21.2	20.1 <sup>a</sup>	20.9	19.4 <sup>bd</sup>	20.7
47 - 48	21.4	20.9	21.2 <sup>c</sup>	19.8 <sup>b</sup>	20.6 <sup>b</sup>
69 - 70	21.9	21.6 <sup>d</sup>	21.4 <sup>d</sup>	20.8 <sup>c</sup>	19.3 <sup>b</sup>
75 - 76	21.6	21.2 <sup>c</sup>	21.7 <sup>d</sup>	19.8 <sup>a</sup>	19.4 <sup>b</sup>

<sup>a</sup> Significant difference from CON1 ( $p \leq 0.05$ )

<sup>b</sup> Significant difference from CON1 ( $p \leq 0.01$ )

<sup>c</sup> Significant difference from CON2 ( $p \leq 0.05$ )

<sup>d</sup> Significant difference from CON2 ( $p \leq 0.01$ )

5. Achieved Compound Intake: The overall mean value for achieved compound intake is summarized in Table 6.

Table 6: Compound Intake (mg/kg/day) for Weeks 0 to 104 (Data taken from page 17 of study)

Sex	300 ppm	750 ppm	1500 ppm
Male	13	32	64
Female	16	41	83

6. Clinical Pathology: Hematology and clinical chemistry evaluations were performed on selected animals (15 animals/sex/group) from each study group during Weeks 26, 52, 78 and 104 of the study. Blood was collected by retroorbital bleeding after an overnight (16 - 24 hrs) fast. Urine samples were collected for a 24-hour interval during Weeks 25, 51, 77 and 103; food and water were available *ad libitum* during the collection. No hematology or clinical chemistry historical control values were included with the study.

a. Hematology: The hematological parameters listed below were evaluated during the study. No consistent effects attributable to treatment were noted during the study for either males or females.

Hematocrit	Reticulocyte count
Hemoglobin	Leukocyte differential count
Leukocyte count	Mean corpuscular hemoglobin
Platelet count	Mean corpuscular hemoglobin conc.
Erythrocyte count	Mean corpuscular volume

Although occasional, statistically significant findings were observed, the magnitude of the responses were not suggestive of biologically significant effects.

b. Clinical Chemistry: The clinical chemistry parameters listed below were evaluated during the study.

Electrolytes

Calcium  
Chloride  
Phosphorous  
Potassium  
Sodium

Enzymes

Alkaline phosphatase (ALP)  
Creatinine phosphokinase (CK)  
Alanine aminotransferase (ALT)  
Aspartate aminotransferase (AST)  
 $\gamma$ -Glutamyl transpeptidase

Other

Albumin  
Blood creatinine  
Blood urea nitrogen  
Total cholesterol  
Globulins  
Glucose  
Total Bilirubin  
Total Protein  
Direct bilirubin  
Indirect bilirubin  
A/G Ratio

Although occasional significant differences were noted, the magnitude of the responses were not great enough to be of biological significance.

c. Urinalysis: The following parameters were measured during the study:

Total volume	Glucose
Specific gravity	Ketone bodies
Protein	Occult blood
Appearance	Urobilirubin
Sediment	Total bilirubin
pH	Specific gravity
Color	

The only significant findings occurred at Week 77, where the high-dose females showed a decreases in total urine volume accompanied by an increase in specific gravity.

7. Ophthalmological examinations: Examinations were performed during the prestudy acclimation period and again before terminal sacrifice. No treatment-related eye lesions were observed. During the prestudy evaluation, a high percentage of the animals exhibited corneal crystals. The corneal crystals were also present at terminal sacrifice, with high incidences in all of the dose groups. The study states that the presence of corneal crystals is common for the strain and age of the animals used in the study.

8. Sacrifice and Pathology: The tissues listed below were fixed in 10% neutral buffered formalin. Tissues from the two control groups and the high-dose group were examined histologically, while the lungs, livers, kidneys and gross lesions were examined for all dose groups. Selected organs (CAPITAL LETTERS) were also weighed. Terminal body weights were also recorded.

<u>Digestive system</u>	<u>Cardiovas./Hematol</u>	<u>Neurologic</u>
Pancreas	Aorta	BRAIN with stem
Salivary gland	HEART	Periph. nerve
Esophagus	Bone marrow	Spinal cord
Stomach	Lymph nodes	Pituitary
Duodenum	SPLEEN	Eyes
Jejunum	Thymus	<u>Glandular</u>
Ileum	<u>Urogenital</u>	Adrenals
Cecum	KIDNEYS	Thyroids
Colon	Urinary bladder	Mammary gland
Rectum	TESTES	<u>Other</u>
LIVER	Ovaries	Gross lesions
Gall Bladder	Prostate	Skin
<u>Respiratory</u>	Uterus	Bone
Lungs	Epididymis	Skeletal muscle
Trachea	Vagina	
	Seminal vesicles	

a. Organ Weights: At terminal sacrifice, body weights and selected organs weights were determined; significant findings are summarized in Table 7. Significant differences (from control 1) were limited to high-dose females and consisted of decreased terminal body weight and increased brain weight, relative to terminal body weight. The higher relative brain weight appears to be a reflection of decreased terminal body weight rather than a treatment-related effect.

Table 7: Terminal Body Weights and Relative Organ Weights (Data summarized from Appendix 3, Tables 1, 4 and 5 of study)

	0 ppm (CON1)	300 ppm	750 ppm	1500 ppm	0 ppm (CON2)
<u>Terminal Body Weights, g</u>					
Male	674	656 (-2.8,-1.5)	688 (2.1,3.4)	656 (-2.9,-1.6)	666
Female	481	459 (-4.6,5.0)	479 (-0.4,9.6)	407 <sup>a</sup> (-15.4,-6.9)	437
<u>Brain Weight Relative to Terminal Body Weight, %</u>					
Female	0.438	0.451	0.436	0.514 <sup>a</sup>	0.484

<sup>1</sup> Values in parentheses represent the percent of control values (% of CON1, % of CON2)

<sup>a</sup> Significant difference from CON1 ( $p \leq 0.01$ )

b. Gross Pathology: Gross necropsy examination of tissues from animals found dead, sacrificed in extremis, or at termination of the study did not reveal any treatment-related findings.

c. Microscopic Pathology: Significant nonneoplastic lesions are summarized in Table 8. At terminal sacrifice, the mesenteric lymph node of high-dose males and females showed increased incidence of blood in the sinuses, hemosiderosis and histiocytosis. Additionally, high-dose females had an increased incidence of bile duct hyperplasia and mononuclear infiltration of the liver.

Although neoplastic lesions were noted, the incidences were comparable among all study groups and not suggestive of any treatment-related effects. A summary of neoplastic lesions is enclosed (Appendix 1).

Table 8: Histopathological Findings (Data taken from Appendix 3, Tables 11 to 16 study)

Observation	0 ppm (CON1)	300 ppm	750 ppm	1500 ppm	0 ppm (CON2)
<i>Mesenteric Lymph Nodes - Males</i>					
Total number examined	57 <sup>1</sup> (36, 21)	4 (1, 3)	5 (3, 2)	57 (33, 24)	54 (29, 25)
Blood in sinuses	1 (1, 0)	2 (1, 1)	1 (0, 1)	11 (8 <sup>a</sup> , 3)	3 (1, 2)
Hemosiderosis	2 (2, 0)	2 (0, 2)	2 (2, 0)	19 (12 <sup>bd</sup> , 7)	2 (1, 1)
Histiocytosis	6 (5, 1)	0 (0, 0)	0 (0, 0)	19 (10 <sup>c</sup> , 9)	5 (2, 3)
<i>Mesenteric Lymph Nodes - Females</i>					
Total number examined	56 (28, 28)	4 (4, 0)	4 (3, 1)	57 (35, 22)	54 (27, 27)
Blood in sinuses	2 (1, 1)	2 (2, -)	1 (1, 0)	12 (7 <sup>a</sup> , 5)	6 (4, 2)
Hemosiderosis	6 (2, 4)	1 (1, -)	2 (1, 1)	25 (16 <sup>b</sup> , 9)	8 (7, 1)
Histiocytosis	12 (4, 8)	2 (2, -)	1 (1, 0)	31 (18 <sup>b</sup> , 13)	17 (10, 7)
<i>Liver - Females</i>					
Total number examined	60 (30, 30)	60 (36, 24)	59 (38, 21)	60 (38, 22)	60 (30, 30)
Bile duct hyperplasia	27 (16, 11)	29 (22, 7)	27 (21, 6)	40 (30 <sup>a</sup> , 10)	27 (19, 8)
Mononuclear infiltration	11 (6, 5)	10 (6, 4)	14 (14, 0)	17 (16 <sup>c</sup> , 1)	10 (5, 5)

<sup>1</sup> Values represent lesion incidence for all animals on study. Numbers in parentheses (X, Y) represent incidence at terminal sacrifice (X) and animals found dead or moribund sacrifices (Y).

<sup>a</sup> Significant difference from CON1 ( $p \leq 0.05$ )

<sup>b</sup> Significant difference from CON1 ( $p \leq 0.01$ )

<sup>c</sup> Significant difference from CON2 ( $p \leq 0.05$ )

<sup>d</sup> Significant difference from CON2 ( $p \leq 0.01$ )

E. DISCUSSION: In this combined chronic toxicity/oncogenicity study, male and female rats were fed diets containing 0, 300, 750 or 1500 ppm test compound (mg/kg/day equivalents: 0, 13, 32, or 64 for males and 0, 16, 41, or 83 for females). No treatment-related effects were noted in either the incidence of clinical signs or deaths. The percent mortalities (excluding accidental deaths) and mean survival times were comparable among all of the study groups.

Although significant decreases were noted in the mean body weights of high-dose males and females, the differences were slight with percent changes generally less than 10% (0.4 to 6.5%, males; 0.6 to 7.3%, females). The significant decreases in food consumption by high-dose animals appears to be a reflection of decreased body weight rather than a treatment-related effect. Hematology, clinical chemistry and urinalysis findings of treated animals were comparable to those of the control.

The incidence of gross pathological findings did not reveal any treatment-related effects. Histopathological evaluation revealed significant increases in the incidence sinusoidal blood, hemosiderosis and histiocytosis in the mesenteric lymph nodes of high-dose males and females. High-dose females also had an increased incidence of bile duct hyperplasia and mononuclear infiltration of the liver.

In a parallel study (MRID No.: 418023-01), male and female CD-1 mice were fed diets containing BARDAC 2280 at concentrations of 0, 100, 500, or 1000 ppm (mg/kg/day equivalents: 0, 15.0, 76.3, or 155.5 for males and 0, 18.6, 93.1, or 193.1 for females). No treatment-related effects were noted in the incidence of clinical signs, deaths, gross and histopathological observations. Hematological values were comparable among all study groups. Effects attributable to treatment included decreased mean body weights and body weight gains of high-dose males and females.

#### F. CONCLUSIONS

Adequacy of the High Dose Tested to Assess Chronic Toxicity and Carcinogenicity: Doses for this study were selected based on a 90-day study (MRID No. 409663-02) which identified a LOEL of 3000 ppm (175 mg/kg/day, males; 226 mg/kg/day, females). The LOEL (highest dose tested, HDT) was based on mortality (80%), decreases in mean body weights, body weight gain and food consumption, alterations in hematology and clinical chemistry parameters, gross pathology (emaciation, hemorrhagic stomachs, decreased spleen size and dilated and distended cecum) and non-neoplastic lesions (glycogen depletion in the liver, splenic contraction, sinus erythrocytosis and lymphoid hyperplasia on the mesenteric lymph nodes).

In the present study, the HDT (1500 ppm  $\approx$  64 mg/kg/day, males; 83 mg/kg/day, females) did not alter survival or result in adverse clinical signs. Animals showed only moderate weight loss. Although males and females showed statistically significant

decreases in mean body weights, the differences were slight (approximately 6%) and did not meet the weight gain depression criteria of 10%. However, this dose induced significantly higher incidences of non-neoplastic lesions in the mesenteric lymph nodes (sinusoidal blood, hemosiderosis and histiocytosis) in both males and females, compared to their respective controls.

These lesions are spontaneous in nature and commonly seen in aging or aged rats and are not considered life-threatening. However, exacerbation of these spontaneous lesions was seen in both sexes of rats found dead, sacrificed moribund and sacrificed at termination. The incidence of these lesions in control males and females were within the normal background range for this age/strain of rats. Therefore, the increased incidence of these lesions is attributed to treatment. Higher dosing might have further increased/exacerbated the incidence and/or severity of these lesions resulting in life-threatening toxicity (i.e. early mortality).

Although the toxic effects predicted from the results of the 90-day study did not materialize and no carcinogenic response was seen, the HDT selected probably could not have been much higher. A dose of 3000 ppm would have resulted in "excessive toxicity" as indicated by the results of the 90-day study. A dose of 2000 ppm may have caused "sufficient toxicity" resulting in additional decrements in body weight gain and exacerbation of the spontaneous non-neoplastic lesions. The HDT (1500 ppm) induced "minimal toxicity" without substantially altering the normal life-span of the animals, indicating that the Maximum Tolerated Dose was "barely" missed. Therefore, it is concluded that the HDT was adequate to assess the chronic toxicity and carcinogenic potential of BARDAC 2280.

Under the conditions of this study, for chronic toxicity a NOEL of 750 ppm (32 mg/kg/day, males; 41 mg/kg/day, females) and a LOEL of 1500 ppm (64 mg/kg/day, males; 83 mg/kg/day, females) is was established. The LOEL was based on moderate decreases in mean body weights and body weight gain and increased incidences of non-neoplastic lesions in the mesenteric lymph nodes (sinusoidal blood, hemosiderosis and histiocytosis). At the dose levels tested, BARDAC 2280 was not carcinogenic in male or female mice.

**CORE CLASSIFICATION:** Minimum This study satisfies guideline requirements [§83-5(a)] for a combined chronic/oncogenicity study in rats and is acceptable for regulatory purposes.

**APPENDIX 1: SUMMARY OF NEOPLASTIC LESIONS (Taken from Appendix 3, Tables 14, 15, 17, 18, 19, and 20 of study)**

TABLE 14  
CHRONIC DIETARY TOXICITY/ONCOGENICITY STUDY WITH  
DIDECYLOIMETHYLAMMONIUMCHLORIDE IN RATS  
SUMMARY OF NEOPLASTIC MICROSCOPIC DIAGNOSES

DATA FOR ALL ANIMALS ON STUDY  
MALES

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	60	60	60	60	60
NUMBER OF ANIMALS	60	60	60	60	60
TOTAL BODY					
TOTAL NUMBER EXAMINED	3	1	1	2	3
#M GRANULOCYTIC LEUKEMIA	0	0	1	0	0
#M HISTIOCYTIC SARCOMA	0	1	0	0	0
#M LYMPHOSARCOMA	2	0	0	2	1
ADIPOSE TISSUE					
TOTAL NUMBER EXAMINED	3	2	4	1	1
#B LIPOMA	3	0	1	0	0
MESENTERY/OMITUM					
TOTAL NUMBER EXAMINED	7	3	3	2	7
MISSING	0	0	0	1	0
#M LYMPHOSARCOMA	1	0	0	0	0
PERITONEAL CAV					
TOTAL NUMBER EXAMINED	0	0	0	0	1
#M LIPOSARCOMA	-	-	-	-	1
PLEURA					
TOTAL NUMBER EXAMINED	0	0	0	0	1
HEART					
TOTAL NUMBER EXAMINED	60	2	3	60	60
EXAMINED, UNREMARKABLE	35	0	1	24	19
#M NEOPLASM, METASTATIC SITE	1	0	0	0	0
#B NEURILEMMOMA	1	0	0	0	0
#M LYMPHOSARCOMA	1	0	0	0	1
AORTA					
TOTAL NUMBER EXAMINED	59	0	3	59	59
EXAMINED, UNREMARKABLE	55	-	0	55	54
MISSING	1	-	0	1	1
#M LYMPHOSARCOMA	0	-	0	0	-
VASCULATURE					
TOTAL NUMBER EXAMINED	0	2	1	2	5
SALIVARY GL					
TOTAL NUMBER EXAMINED	59	3	1	58	59
EXAMINED, UNREMARKABLE	55	2	1	55	57
TOO AUTOLYZED TO EVALUATE	1	0	0	0	1
MISSING	0	0	0	2	0
#M LYMPHOSARCOMA	1	0	0	1	0

GROUP LEGEND: 1 is 0 PPM, 2 is 300 PPM, 3 is 750 PPM, 4 is 1500 PPM, 5 is 0 PPM

TABLE 14 (Continued)  
CHRONIC DIETARY TOXICITY/ONCOGENICITY STUDY WITH  
DIDECYLDIMETHYLAMMONIUMCHLORIDE IN RATS  
SUMMARY OF NEOPLASTIC MICROSCOPIC DIAGNOSES

DATA FOR ALL ANIMALS ON STUDY  
MALES

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	60	60	60	60	60
NUMBER OF ANIMALS	60	60	60	60	60
ORAL/PHARYNGEAL					
TOTAL NUMBER EXAMINED	0	2	0	0	1
EXAMINED, UNREMARKABLE	-	1	-	-	0
ESOPHAGUS					
TOTAL NUMBER EXAMINED	60	2	4	60	60
EXAMINED, UNREMARKABLE	58	2	4	58	58
STOMACH					
TOTAL NUMBER EXAMINED	60	14	12	58	59
EXAMINED, UNREMARKABLE	37	7	4	30	38
TOO AUTOLYZED TO EVALUATE	0	0	0	0	1
MISSING	0	0	0	2	0
# LEIOMYOSARCOMA	0	0	0	0	1
# LYMPHOSARCOMA	1	0	0	0	1
LIVER					
TOTAL NUMBER EXAMINED	60	60	59	60	60
EXAMINED, UNREMARKABLE	3	8	7	6	7
# HEPATOCELLULAR ADENOMA	3	2	4	3	3
# HEPATOCELLULAR CARCINOMA	0	0	0	1	0
# NEOPLASM, METASTATIC SITE	0	0	1	0	0
# CARCINOMA OF BILE DUCTS	0	0	0	0	1
# UNDIFFERENTIATED SARCOMA	0	0	0	0	1
# HISTIOCYTIC SARCOMA	1	1	0	0	0
# GRANULOCYTIC LEUKEMIA	0	0	1	0	0
# LYMPHOSARCOMA	1	0	0	2	1
PANCREAS					
TOTAL NUMBER EXAMINED	59	4	5	60	59
EXAMINED, UNREMARKABLE	24	2	0	37	34
TOO AUTOLYZED TO EVALUATE	-	0	0	0	-
# ADENOMA OF EXOCRINE CELLS	0	1	0	1	0
# ADENOMA OF ENDOCRINE CELLS	1	2	3	5	8
# LYMPHOSARCOMA	1	0	0	0	0
DUODENUM					
TOTAL NUMBER EXAMINED	54	0	2	58	53
EXAMINED, UNREMARKABLE	53	-	2	53	53
TOO AUTOLYZED TO EVALUATE	6	-	0	4	7
# LYMPHOSARCOMA	0	-	0	1	0
JEJUNUM					
TOTAL NUMBER EXAMINED	48	0	1	52	48
EXAMINED, UNREMARKABLE	48	-	1	52	48
TOO AUTOLYZED TO EVALUATE	12	-	3	8	12

GROUP LEGEND: 1 is 0 PPM, 2 is 300 PPM, 3 is 750 PPM, 4 is 1500 PPM, 5 is 0 PPM

TABLE 14 (Continued)  
CHRONIC DIETARY TOXICITY/ONCOGENICITY STUDY WITH  
DIDECYLDIMETHYLAMMONIUMCHLORIDE IN RATS  
SUMMARY OF NEOPLASTIC MICROSCOPIC DIAGNOSES

DATA FOR ALL ANIMALS ON STUDY  
MALES

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	60	60	60	60	60
NUMBER OF ANIMALS	60	60	60	60	60
ILEUM					
TOTAL NUMBER EXAMINED	50	1	1	50	50
EXAMINED, UNREMARKABLE	48	1	1	50	48
TOO AUTOLYZED TO EVALUATE	10	0	3	10	10
#M LYMPHOSARCOMA	0	0	0	0	1
CECUM					
TOTAL NUMBER EXAMINED	49	3	3	51	49
EXAMINED, UNREMARKABLE	48	3	1	50	49
TOO AUTOLYZED TO EVALUATE	11	1	0	9	10
MISSING	0	0	0	0	1
COLON					
TOTAL NUMBER EXAMINED	56	1	0	55	54
EXAMINED, UNREMARKABLE	54	1	-	55	53
TOO AUTOLYZED TO EVALUATE	3	0	1	5	6
MISSING	1	0	-	0	0
RECTUM					
TOTAL NUMBER EXAMINED	55	1	0	54	51
EXAMINED, UNREMARKABLE	54	1	-	53	50
TOO AUTOLYZED TO EVALUATE	4	0	-	6	9
MISSING	1	0	-	0	0
PITUITARY					
TOTAL NUMBER EXAMINED	60	38	45	60	56
EXAMINED, UNREMARKABLE	5	-	0	10	3
TOO AUTOLYZED TO EVALUATE	0	0	1	0	-
MISSING	0	0	0	0	3
#B ADENOMA	48	37	45	44	45
#M CARCINOMA	0	0	0	0	1
#M LYMPHOSARCOMA	1	0	0	2	0
THYROID GL					
TOTAL NUMBER EXAMINED	59	3	11	58	59
EXAMINED, UNREMARKABLE	31	-	4	29	45
TOO AUTOLYZED TO EVALUATE	0	0	0	2	1
MISSING	1	0	0	0	0
#B ADENOMA OF FOLLICULAR CELLS	3	0	2	5	1
#M ADENOCARCINOMA OF FOLLICULAR CELLS	1	0	1	2	1
#B ADENOMA OF PARAFOLLICULAR CELLS	1	-	2	0	3
#M LYMPHOSARCOMA	1	0	0	0	0
PARATHYROID GL					
TOTAL NUMBER EXAMINED	49	2	7	58	53
EXAMINED, UNREMARKABLE	31	1	1	29	29
MISSING	11	0	0	2	7

GROUP LEGEND: 1 is 0 PPM, 2 is 300 PPM, 3 is 750 PPM, 4 is 1500 PPM, 5 is 0 PPM

TABLE 14 (Continued)  
CHRONIC DIETARY TOXICITY/ONCOGENICITY STUDY WITH  
DIDECYLDIMETHYLAMMONIUMCHLORIDE IN RATS  
SUMMARY OF NEOPLASTIC MICROSCOPIC DIAGNOSES

DATA FOR ALL ANIMALS ON STUDY  
MALES

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	60	60	60	60	60
NUMBER OF ANIMALS	60	60	60	60	60
PARATHYROID GL (CONTINUED)					
#B ADENOMA	2	0	1	1	2
#M LYMPHOSARCOMA	1	0	0	0	0
ADRENAL GL					
TOTAL NUMBER EXAMINED	60	25	27	60	60
EXAMINED, UNREMARKABLE	12	2	1	18	13
MISSING	0	0	1	0	0
#B ADENOMA OF CORTICAL CELLS	1	4	1	1	5
#M CARCINOMA OF CORTICAL CELLS	0	1	0	0	0
#B PHEOCHROMOCYTOMA	14	8	7	6	9
#M PHEOCHROMOCYTOMA	0	0	0	1	0
#M LYMPHOSARCOMA	1	0	0	1	0
SKIN					
TOTAL NUMBER EXAMINED	60	25	25	60	60
EXAMINED, UNREMARKABLE	48	1	2	41	39
TOO AUTOLYZED TO EVALUATE	3	0	1	3	0
MISSING	0	1	0	0	0
#B PAPILLOMA	0	3	0	2	2
#B ADENOMA OF BASAL CELLS	0	0	1	0	0
#M LYMPHOSARCOMA	1	0	0	0	0
SUBCUTIS					
TOTAL NUMBER EXAMINED	3	7	4	2	5
EXAMINED, UNREMARKABLE	1	0	1	0	0
#B FIBROMA	2	1	1	1	0
#M UNDIFFERENTIATED SARCOMA	0	1	0	0	2
#M UNDIFFERENTIATED CARCINOMA	0	1	0	0	1
#M OSTEOSARCOMA	0	0	0	1	0
#B LIPOMA	0	1	2	0	0
#M LYMPHOSARCOMA	0	0	0	1	0
HEAD					
TOTAL NUMBER EXAMINED	0	1	1	0	1
MISSING	-	0	1	-	0
#M UNDIFFERENTIATED CARCINOMA	-	1	0	-	0
#M ADENOCARCINOMA	-	0	1	-	0
EARS					
TOTAL NUMBER EXAMINED	2	0	1	0	0
EXAMINED, UNREMARKABLE	1	-	0	-	-
#B PAPILLOMA	1	-	0	-	-
AUD SEBACEOUS GL					
TOTAL NUMBER EXAMINED	0	0	0	1	0
#M ADENOCARCINOMA	-	-	-	1	-

GROUP LEGEND: 1 is 0 PPM, 2 is 300 PPM, 3 is 750 PPM, 4 is 1500 PPM, 5 is 0 PPM

TABLE 14 (Continued)  
CHRONIC DIETARY TOXICITY/ONCOGENICITY STUDY WITH  
DIDECYLDIMETHYLAMMONIUMCHLORIDE IN RATS  
SUMMARY OF NEOPLASTIC MICROSCOPIC DIAGNOSES

DATA FOR ALL ANIMALS ON STUDY  
MALES

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	60	60	60	60	60
NUMBER OF ANIMALS	60	60	60	60	60
NARES/NOSE					
TOTAL NUMBER EXAMINED	6	7	3	6	6
EXAMINED, UNREMARKABLE	4	1	1	4	1
MAMMARY GL					
TOTAL NUMBER EXAMINED	18	5	5	16	11
EXAMINED, UNREMARKABLE	0	0	1	1	3
MISSING	2	3	0	1	0
#B ADENOMA	1	1	1	0	0
#B FIBROADENOMA	0	0	0	2	0
#B CYSTADENOMA	0	1	0	0	0
PAWS/FEET					
TOTAL NUMBER EXAMINED	16	24	21	18	27
EXAMINED, UNREMARKABLE	1	0	0	0	1
MISSING	3	0	0	0	2
TAIL					
TOTAL NUMBER EXAMINED	5	2	5	4	4
EXAMINED, UNREMARKABLE	0	0	0	1	0
SPLEEN					
TOTAL NUMBER EXAMINED	60	12	16	60	60
EXAMINED, UNREMARKABLE	30	4	3	36	38
#M GRANULOCYTIC LEUKEMIA	0	0	1	0	0
#M UNDIFFERENTIATED SARCOMA	0	1	0	0	0
#M HISTIOCYTIC SARCOMA	0	1	0	0	0
#M FIBROUS HISTIOCYTOMA	0	0	0	0	1
#M LYMPHOSARCOMA	2	0	0	2	1
LYMPH NO. S-MAN					
TOTAL NUMBER EXAMINED	60	11	11	58	58
EXAMINED, UNREMARKABLE	20	1	0	27	27
TOO AUTOLYZED TO EVALUATE	0	0	1	0	0
MISSING	0	0	1	2	2
#M LYMPHOSARCOMA	1	0	0	1	1
LYMPH NO. MED					
TOTAL NUMBER EXAMINED	11	6	12	11	17
EXAMINED, UNREMARKABLE	0	0	1	0	0
MISSING	0	0	1	0	1
#M HISTIOCYTIC SARCOMA	0	1	0	0	0
#M LYMPHOSARCOMA	0	0	1	2	0
LYMPH NO. MES					
TOTAL NUMBER EXAMINED	57	4	5	57	54
EXAMINED, UNREMARKABLE	41	0	1	25	37
TOO AUTOLYZED TO EVALUATE	2	0	0	2	1
MISSING	1	0	0	1	5

GROUP LEGEND: 1 is 0 PPM, 2 is 300 PPM, 3 is 750 PPM, 4 is 1500 PPM, 5 is 0 PPM

TABLE 14 (Continued)  
CHRONIC DIETARY TOXICITY/ONCOGENICITY STUDY WITH  
DIDECYLDIMETHYLAMMONIUMCHLORIDE IN RATS  
SUMMARY OF NEOPLASTIC MICROSCOPIC DIAGNOSES

DATA FOR ALL ANIMALS ON STUDY  
MALES

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	60	60	60	60	60
NUMBER OF ANIMALS	60	60	60	60	60
LYMPH NO. MES (CONTINUED)					
#M GRANULOCYTIC LEUKEMIA	0	0	1	0	0
#M FIBROUS HISTIOCYTOMA	0	0	0	0	1
#M LYMPHOSARCOMA	1	0	0	2	1
LYMPH NO. REN					
TOTAL NUMBER EXAMINED	3	4	5	6	5
MISSING	0	1	0	0	1
#M GRANULOCYTIC LEUKEMIA	0	0	1	0	0
#M LYMPHOSARCOMA	1	0	0	2	1
LYMPH NO. PANC					
TOTAL NUMBER EXAMINED	3	1	1	3	2
EXAMINED, UNREMARKABLE	0	0	0	1	2
MISSING	0	3	4	0	1
#M LYMPHOSARCOMA	1	0	0	1	0
LYMPH NO. OTHER					
TOTAL NUMBER EXAMINED	5	7	8	8	14
MISSING	0	0	1	0	1
#M GRANULOCYTIC LEUKEMIA	0	0	1	0	0
#M LYMPHOSARCOMA	1	0	0	2	0
THYMIC REGION					
TOTAL NUMBER EXAMINED	60	2	4	59	60
EXAMINED, UNREMARKABLE	55	1	1	56	57
TOO AUTOLYZED TO EVALUATE	0	0	0	1	0
#M GRANULOCYTIC LEUKEMIA	0	0	1	0	0
#M LYMPHOSARCOMA	1	0	0	1	1
BONE/JOINT					
TOTAL NUMBER EXAMINED	0	1	0	1	2
MISSING	-	0	-	0	0
BONE, STERNUM					
TOTAL NUMBER EXAMINED	59	0	0	59	59
EXAMINED, UNREMARKABLE	56	-	-	57	57
MISSING	-	-	-	1	1
BONE, FEMUR					
TOTAL NUMBER EXAMINED	60	0	-	60	60
EXAMINED, UNREMARKABLE	55	-	-	57	57
BONE, VERTEBRA					
TOTAL NUMBER EXAMINED	0	1	3	1	1
EXAMINED, UNREMARKABLE	-	1	1	0	1

GROUP LEGEND: 1 is 0 PPM, 2 is 300 PPM, 3 is 750 PPM, 4 is 1500 PPM, 5 is 0 PPM

TABLE 14 (Continued)  
CHRONIC DIETARY TOXICITY/ONCOGENICITY STUDY WITH  
DIDECYLDIMETHYLAMMONIUMCHLORIDE IN RATS  
SUMMARY OF NEOPLASTIC MICROSCOPIC DIAGNOSES

DATA FOR ALL ANIMALS ON STUDY  
MALES

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	60	60	60	60	60
NUMBER OF ANIMALS	60	60	60	60	60
BONE, VERTEBRA (CONTINUED)					
#M OSTEOSARCOMA	-	0	1	0	0
BONE MARROW					
TOTAL NUMBER EXAMINED	60	0	0	58	60
EXAMINED, UNREMARKABLE	53	-	-	55	55
TOO AUTOLYZED TO EVALUATE	0	-	-	2	0
#M LYMPHOSARCOMA	2	-	-	1	1
SKELETAL MUSCLE					
TOTAL NUMBER EXAMINED	60	4	2	60	60
EXAMINED, UNREMARKABLE	51	0	0	46	50
#M LYMPHOSARCOMA	0	0	0	1	0
BRAIN					
TOTAL NUMBER EXAMINED	58	17	18	60	59
EXAMINED, UNREMARKABLE	52	14	12	57	53
TOO AUTOLYZED TO EVALUATE	1	0	0	0	0
MISSING	1	0	0	0	1
#M NEOPLASM, METASTATIC SITE	0	0	0	0	1
#B GRANULAR CELL TUMOR	0	-	0	0	0
#M EPENDYMOMA	0	0	0	0	1
#M LYMPHOSARCOMA	1	0	0	1	0
SPINAL CORD					
TOTAL NUMBER EXAMINED	59	1	0	59	59
EXAMINED, UNREMARKABLE	55	-	-	57	56
TOO AUTOLYZED TO EVALUATE	1	-	-	1	0
MISSING	0	-	-	0	1
NERVE, SCIATIC					
TOTAL NUMBER EXAMINED	60	0	0	60	59
EXAMINED, UNREMARKABLE	55	-	-	59	59
MISSING	0	-	-	0	1
#M LYMPHOSARCOMA	1	-	-	0	0
EYE					
TOTAL NUMBER EXAMINED	58	16	12	58	57
EXAMINED, UNREMARKABLE	51	14	7	49	51
TOO AUTOLYZED TO EVALUATE	2	0	0	2	2
MISSING	0	0	0	0	1
#M LYMPHOSARCOMA	0	0	0	1	0
LACRYMAL GL					
TOTAL NUMBER EXAMINED	3	3	6	5	6
EXAMINED, UNREMARKABLE	1	2	3	2	3

GROUP LEGEND: 1 is 0 PPM, 2 is 300 PPM, 3 is 750 PPM, 4 is 1500 PPM, 5 is 0 PPM

TABLE 14 (Continued)  
CHRONIC DIETARY TOXICITY/ONCOGENICITY STUDY WITH  
DIDECYLDIMETHYLAMMONIUMCHLORIDE IN RATS  
SUMMARY OF NEOPLASTIC MICROSCOPIC DIAGNOSES

DATA FOR ALL ANIMALS ON STUDY  
MALES

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	60	60	60	60	60
NUMBER OF ANIMALS	60	60	60	60	60
TESTES					
TOTAL NUMBER EXAMINED	60	58	28	60	60
EXAMINED, UNREMARKABLE	24	0	1	29	25
#B ADENOMA OF INTERSTITIAL CELLS	3	1	5	7	3
#M NEOPLASM, METASTATIC SITE	1	0	0	0	0
#B MESOTHELIOMA	0	0	0	1	0
#M LYMPHOSARCOMA	0	0	0	1	0
EPIDIDYMIDES					
TOTAL NUMBER EXAMINED	60	6	24	60	60
EXAMINED, UNREMARKABLE	36	3	9	29	30
SEMINAL VESICLE					
TOTAL NUMBER EXAMINED	54	8	17	57	56
EXAMINED, UNREMARKABLE	34	1	2	41	34
TOO AUTOLYZED TO EVALUATE	6	0	1	3	4
#M LYMPHOSARCOMA	1	0	0	0	0
PROSTATE					
TOTAL NUMBER EXAMINED	59	2	12	60	60
EXAMINED, UNREMARKABLE	21	0	0	24	24
TOO AUTOLYZED TO EVALUATE	1	0	0	0	0
#M SQUAMOUS CELL CARCINOMA	0	0	1	0	0
#M LYMPHOSARCOMA	1	0	0	1	0
PENIS					
TOTAL NUMBER EXAMINED	0	0	0	1	0
EXAMINED, UNREMARKABLE	-	-	-	1	-
NASAL CAVITY					
TOTAL NUMBER EXAMINED	1	2	1	0	0
EXAMINED, UNREMARKABLE	1	2	1	-	-
TRACHEA					
TOTAL NUMBER EXAMINED	60	2	6	60	60
EXAMINED, UNREMARKABLE	14	1	2	23	17
#M NEOPLASM, METASTATIC SITE	1	0	0	0	0
#M LYMPHOSARCOMA	1	0	0	1	0
LUNGS					
TOTAL NUMBER EXAMINED	60	60	60	60	60
EXAMINED, UNREMARKABLE	37	29	24	30	30
#B ADENOMA	1	0	0	1	0
#M NEOPLASM, METASTATIC SITE	0	2	1	2	0
#M GRANULOCYTIC LEUKEMIA	0	0	1	0	0

GROUP LEGEND: 1 - 0 ppm, 2 - 300 ppm, 3 - 750 ppm, 4 - 1500 ppm, 5 - 0 ppm

TABLE 14 (Continued)  
 CHRONIC DIETARY TOXICITY/ONCOGENICITY STUDY WITH  
 DIDECYLDIMETHYLAMMONIUMCHLORIDE IN RATS  
 SUMMARY OF NEOPLASTIC MICROSCOPIC DIAGNOSES

DATA FOR ALL ANIMALS ON STUDY  
 MALES

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	60	60	60	60	60
NUMBER OF ANIMALS	60	60	60	60	60
LUNGS (CONTINUED)					
#M LYMPHOSARCOMA	1	0	0	1	1
KIDNEYS					
TOTAL NUMBER EXAMINED	58	60	60	60	60
EXAMINED, UNREMARKABLE	0	5	2	5	3
TOO AUTOLYZED TO EVALUATE	2	0	0	0	0
#M TUBULAR CARCINOMA	0	0	1	0	0
#M GRANULOCYTIC LEUKEMIA	0	0	1	0	0
#B RENAL LIPOMA	0	0	0	1	0
#B LIPOMA	0	0	0	0	1
#M RENAL MESENCHYMAL TUMOR	0	0	1	0	0
#M LYMPHOSARCOMA	1	0	0	1	1
URINARY BLADDER					
TOTAL NUMBER EXAMINED	59	4	9	59	60
EXAMINED, UNREMARKABLE	50	1	8	53	53
TOO AUTOLYZED TO EVALUATE	1	0	0	1	0
#M LYMPHOSARCOMA	1	0	0	0	0
URETHRA					
TOTAL NUMBER EXAMINED	0	0	1	0	0

GROUP LEGEND: 1 is 0 ppm, 2 is 300 ppm, 3 is 750 ppm, 4 is 1500 ppm, 5 is 0 ppm

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TABLE 15  
CHRONIC DIETARY TOXICITY/ONCOGENICITY STUDY WITH  
DIDECYLDIMETHYLAMMONIUMCHLORIDE IN RATS  
SUMMARY OF MICROSCOPIC DIAGNOSES

ANIMALS SACRIFICED AT WEEK 104  
FEMALES

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	60	60	60	60	60
NUMBER OF ANIMALS SACRIFICED	30	36	39	38	30
TOTAL BODY					
TOTAL NUMBER EXAMINED	2	0	2	0	0
EXAMINED, UNREMARKABLE	0	-	1	-	-
#M FIBROUS HISTIOCYTOMA	2	-	0	-	-
#M LYMPHOSARCOMA	0	-	1	-	-
ADIPOSE TISSUE					
TOTAL NUMBER EXAMINED	2	3	1	2	4
EXAMINED, UNREMARKABLE	0	0	0	1	1
FIBROSIS	1	1	0	1	1
NECROSIS	1	0	0	0	0
STEATITIS	0	0	0	1	1
#B LIPOMA	1	2	1	0	1
MESENTERY/OMITUM					
TOTAL NUMBER EXAMINED	1	0	1	0	0
FIBROSIS	0	-	1	-	-
VASCULITIS	1	-	1	-	-
ARTERIAL MEDIAL HYPERPLASIA	0	-	1	-	-
HEART					
TOTAL NUMBER EXAMINED	30	0	0	38	30
EXAMINED, UNREMARKABLE	16	-	-	28	20
VACUOLATION	0	-	-	1	0
MYOFIBRILLAR DEGENERATION	4	-	-	5	4
FIBROSIS	12	-	-	7	9
INFILTRATION BY MAST CELLS	1	-	-	0	0
MYOCARDITIS	1	-	-	0	0
AORTA					
TOTAL NUMBER EXAMINED	30	0	0	37	30
EXAMINED, UNREMARKABLE	30	-	-	37	30
MISSING	0	-	-	1	0
SALIVARY GL					
TOTAL NUMBER EXAMINED	29	0	0	38	29
EXAMINED, UNREMARKABLE	29	-	-	37	29
MISSING	1	-	-	0	1

GROUP LEGEND: 1 is 0 PPM, 2 is 300 PPM, 3 is 750 PPM, 4 is 1500 PPM, 5 is 0 PPM

None significantly different from control group

TABLE 17 (Continued)  
CHRONIC DIETARY TOXICITY/ONCOGENICITY STUDY WITH  
DIDECYLDIMETHYLAMMONIUMCHLORIDE IN RATS  
SUMMARY OF MICROSCOPIC DIAGNOSES

DATA FOR ALL ANIMALS ON STUDY  
FEMALES

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	60	60	60	60	60
NUMBER OF ANIMALS	60	60	60	60	60
KIDNEYS (CONTINUED)					
HYPERPLASIA OF TRANSITIONAL EPITHELIUM	4	14	17	4	7
HYPERKERATOSIS	0	0	0	0	1
TUBULAR BASOPHILIA	0	2	3	1	2
CHRONIC PROGRESSIVE NEPHROSIS	14	24	16	20	13
PROTEIN IN TUBULES	16	3	8	4	8
SQUAMOUS METAPLASIA OF TRANSITIONAL EPITHELIUM	0	0	0	0	1
#M NEOPLASM, METASTATIC SITE	1	0	0	0	1
#M LYMPHOSARCOMA	0	0	0	1	0
URETER					
TOTAL NUMBER EXAMINED	1	0	0	0	2
DILATION/DISTENTION	0	-	-	-	1
URETERITIS	1	-	-	-	0
HYPERPLASIA OF TRANSITIONAL EPITHELIUM	1	-	-	-	1
URINARY BLADDER					
TOTAL NUMBER EXAMINED	59	3	0	56	57
EXAMINED, UNREMARKABLE	55	3	-	52	51
TOO AUTOLYZED TO EVALUATE	0	0	-	2	0
MISSING	1	0	-	2	3
EDEMA	0	0	-	2	4
FIBROSIS	1	0	-	1	0
CYSTITIS	4	0	-	2	2
HYPERPLASIA	2	0	-	1	1
SQUAMOUS METAPLASIA	0	0	-	1	1
CAUSE OF DEATH					
TOTAL NUMBER EXAMINED	20	24	21	21	29
UNDETERMINED	1	3	5	3	2
PERITONITIS	0	0	0	1	1
ADENOMA OF THE PITUITARY	22	19	15	14	18
INFLAMMATION OF THE URINARY TRACT	2	0	0	0	0
OBSTRUCTION OF THE URINARY TRACT	0	0	0	0	2
INFLAMMATION OF THE REPRODUCTIVE TRACT	0	1	0	0	0
MASSIVE BENIGN NEOPLASM	1	1	0	1	1
MALIGNANT NEOPLASM	3	0	0	1	5
LYMPHOSARCOMA	0	0	1	1	0

GROUP LEGEND: 1 is 0 ppm, 2 is 300 ppm, 3 is 750 ppm, 4 is 1500 ppm, 5 is 0 ppm

TABLE 18  
CHRONIC DIETARY TOXICITY/ONCOGENICITY STUDY WITH  
DIDECYLDIMETHYLAMMONIUMCHLORIDE IN RATS  
SUMMARY OF NEOPLASTIC MICROSCOPIC DIAGNOSES

DATA FOR ALL ANIMALS ON STUDY  
FEMALES

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	60	60	60	60	60
NUMBER OF ANIMALS	60	60	60	60	60
TOTAL BODY					
TOTAL NUMBER EXAMINED	3	3	3	3	1
EXAMINED, UNREMARKABLE	0	-	1	0	0
#M NEOPLASM, METASTATIC SITE	0	-	0	0	1
#M FIBROUS HISTIOCYTOMA	2	-	0	2	0
#M HISTIOCYTIC SARCOMA	1	-	0	0	0
#M LYMPHOSARCOMA	0	-	2	1	0
ADIPOSE TISSUE					
TOTAL NUMBER EXAMINED	3	3	2	4	6
EXAMINED, UNREMARKABLE	0	0	0	2	1
#B LIPOMA	2	2	1	1	3
MESENTERY/OMITUM					
TOTAL NUMBER EXAMINED	2	1	1	2	2
#M NEOPLASM, METASTATIC SITE	1	0	0	1	1
PERITONEUM					
TOTAL NUMBER EXAMINED	0	0	0	1	0
PERITONEAL CAV					
TOTAL NUMBER EXAMINED	0	0	0	0	1
HEART					
TOTAL NUMBER EXAMINED	60	-	0	60	60
EXAMINED, UNREMARKABLE	35	0	-	42	42
#B NEURILEMMOMA	0	0	-	0	1
AORTA					
TOTAL NUMBER EXAMINED	56	0	0	57	59
EXAMINED, UNREMARKABLE	53	-	-	57	57
MISSING	4	-	-	3	1
VASCULATURE					
TOTAL NUMBER EXAMINED	0	0	0	0	1

GROUP LEGEND: 1 is 0 PPM, 2 is 300 PPM, 3 is 750 PPM, 4 is 1500 PPM, 5 is 0 PPM

TABLE 18 (Continued)  
CHRONIC DIETARY TOXICITY/ONCOGENICITY STUDY WITH  
DIDECYLDIMETHYLAMMONIUMCHLORIDE IN RATS  
SUMMARY OF NEOPLASTIC MICROSCOPIC DIAGNOSES

DATA FOR ALL ANIMALS ON STUDY  
FEMALES

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	60	60	60	60	60
NUMBER OF ANIMALS	60	60	60	60	60
SALIVARY GL					
TOTAL NUMBER EXAMINED	58	0	0	60	58
EXAMINED, UNREMARKABLE	58	-	-	59	58
MISSING	2	-	-	0	2
ESOPHAGUS					
TOTAL NUMBER EXAMINED	60	2	1	60	60
EXAMINED, UNREMARKABLE	53	2	1	58	58
STOMACH					
TOTAL NUMBER EXAMINED	58	7	9	59	59
EXAMINED, UNREMARKABLE	36	0	2	34	36
TOO AUTOLYZED TO EVALUATE	0	0	0	1	0
MISSING	2	0	0	0	1
LIVER					
TOTAL NUMBER EXAMINED	60	60	59	60	60
EXAMINED, UNREMARKABLE	10	16	13	10	15
MISSING	0	0	1	0	0
#B HEPATOCELLULAR ADENOMA	-	2	1	4	0
#B ADENOMA OF BILE DUCTS	0	0	0	0	-
#M FIBROUS HISTIOCYTOMA	-	0	0	2	-
#M HISTIOCYTIC SARCOMA	1	0	0	0	0
#M LYMPHOSARCOMA	0	0	3	1	0
PANCREAS					
TOTAL NUMBER EXAMINED	60	1	4	59	60
EXAMINED, UNREMARKABLE	50	0	1	53	50
TOO AUTOLYZED TO EVALUATE	0	0	0	1	0
#M ADENOCARCINOMA OF ENDOCRINE CELLS	1	0	0	0	-
#B ADENOMA OF ENDOCRINE CELLS	1	0	3	3	3
DUODENUM					
TOTAL NUMBER EXAMINED	58	2	0	55	57
EXAMINED, UNREMARKABLE	58	2	-	55	56
TOO AUTOLYZED TO EVALUATE	-	0	-	4	3
MISSING	0	0	-	1	0

GROUP LEGEND: 1 is 0 ppm, 2 is 300 ppm, 3 is 750 ppm, 4 is 1500 ppm, 5 is 0 ppm

TABLE 18 (Continued)  
CHRONIC DIETARY TOXICITY/ONCOGENICITY STUDY WITH  
DIDECYLDIMETHYLAMMONIUMCHLORIDE IN RATS  
SUMMARY OF NEOPLASTIC MICROSCOPIC DIAGNOSES

DATA FOR ALL ANIMALS ON STUDY  
FEMALES

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	60	60	60	60	60
NUMBER OF ANIMALS	60	60	60	60	60
DUODENUM (CONTINUED)					
# NEOPLASM, METASTATIC SITE	1	0	-	0	0
JEJUNUM					
TOTAL NUMBER EXAMINED	54	2	1	54	53
EXAMINED, UNREMARKABLE	54	1	1	53	53
TOO AUTOLYZED TO EVALUATE	6	1	0	5	5
MISSING	0	0	0	1	1
ILEUM					
TOTAL NUMBER EXAMINED	58	1	0	56	54
EXAMINED, UNREMARKABLE	58	1	-	55	54
TOO AUTOLYZED TO EVALUATE	2	1	-	4	5
MISSING	0	0	-	0	1
# FIBROUS HISTIOCYTOMA	0	0	-	1	0
CECUM					
TOTAL NUMBER EXAMINED	57	2	2	55	54
EXAMINED, UNREMARKABLE	56	2	2	55	53
TOO AUTOLYZED TO EVALUATE	3	2	0	4	4
MISSING	0	0	0	1	2
COLON					
TOTAL NUMBER EXAMINED	58	0	1	57	57
EXAMINED, UNREMARKABLE	57	-	0	57	57
TOO AUTOLYZED TO EVALUATE	1	-	1	3	1
RECTUM					
TOTAL NUMBER EXAMINED	58	0	0	57	57
EXAMINED, UNREMARKABLE	58	-	-	57	57
TOO AUTOLYZED TO EVALUATE	0	-	-	3	1
DUODENUM					
TOTAL NUMBER EXAMINED	59	55	54	60	60
EXAMINED, UNREMARKABLE	5	0	0	8	5
MISSING	-	0	1	0	0

GROUP LEGEND: 1 is 0 PPM, 2 is 300 PPM, 3 is 750 PPM, 4 is 1500 PPM, 5 is 0 PPM

TABLE 18 (Continued)  
CHRONIC DIETARY TOXICITY/ONCOGENICITY STUDY WITH  
DIDECYLDIMETHYLAMMONIUMCHLORIDE IN RATS  
SUMMARY OF NEOPLASTIC MICROSCOPIC DIAGNOSES

DATA FOR ALL ANIMALS ON STUDY  
FEMALES

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	60	60	60	60	60
NUMBER OF ANIMALS	60	60	60	60	60
PITUITARY (CONTINUED)					
#S ADENOMA	50	57	53	50	51
#M CARCINOMA	2	0	1	1	2
THYROID GL					
TOTAL NUMBER EXAMINED	60	1	3	60	60
EXAMINED, UNREMARKABLE	41	0	2	41	36
MISSING	0	1	0	0	0
#S FOLLICULAR ADENOMA	2	1	0	4	2
#M ADENOCARCINOMA OF FOLLICULAR CELLS	0	0	0	1	0
#S ADENOMA OF PARAFOLLICULAR CELLS	6	1	0	5	4
#M CARCINOMA OF PARAFOLLICULAR CELLS	0	0	0	0	2
PARATHYROID GL					
TOTAL NUMBER EXAMINED	46	1	3	54	52
EXAMINED, UNREMARKABLE	44	1	3	53	50
MISSING	14	0	0	5	8
#S ADENOMA	1	0	0	1	1
ADRENAL GL					
TOTAL NUMBER EXAMINED	60	49	41	60	60
EXAMINED, UNREMARKABLE	3	0	0	0	3
MISSING	0	0	1	0	0
#S ADENOMA OF CORTICAL CELLS	19	28	25	23	27
#M NEOPLASM, METASTATIC SITE	0	0	0	0	2
#S PHEOCHROMOCYTOMA	2	3	3	2	0
SKIN					
TOTAL NUMBER EXAMINED	60	31	21	59	60
EXAMINED, UNREMARKABLE	46	10	8	42	43
MISSING	0	0	0	1	0
#S ADENOMA OF BASAL CELLS	0	0	1	0	0
#M FIBROUS HISTIOCYTOMA	0	0	0	1	0
SUBCUTIS					
TOTAL NUMBER EXAMINED	1	0	0	4	4

GROUP LEGEND: 1 is 0 PPM, 2 is 300 PPM, 3 is 750 PPM, 4 is 1500 PPM, 5 is 0 PPM

TABLE 18 (Continued)  
CHRONIC DIETARY TOXICITY/ONCOGENICITY STUDY WITH  
DIDECYLDIMETHYLAMMONIUMCHLORIDE IN RATS  
SUMMARY OF NEOPLASTIC MICROSCOPIC DIAGNOSES

DATA FOR ALL ANIMALS ON STUDY  
FEMALES

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	60	60	60	60	60
NUMBER OF ANIMALS	60	60	60	60	60
SUBCUTIS (CONTINUED)					
#B FIBROMA	0	-	-	2	1
#M MYXOSARCOMA	0	-	-	0	1
#M FIBROUS HISTIOCYTOMA	1	-	-	1	0
#M UNDIFFERENTIATED SARCOMA	0	-	-	0	1
#M LYMPHOSARCOMA	0	-	-	1	0
HEAD					
TOTAL NUMBER EXAMINED	0	0	1	0	0
EXAMINED, UNREMARKABLE	-	-	1	-	-
EARS					
TOTAL NUMBER EXAMINED	0	0	0	0	2
NARES/NOSE					
TOTAL NUMBER EXAMINED	5	0	7	8	8
EXAMINED, UNREMARKABLE	1	-	6	2	6
MAMMARY GL					
TOTAL NUMBER EXAMINED	52	31	33	60	60
EXAMINED, UNREMARKABLE	26	1	2	27	29
MISSING	8	0	0	0	0
#B ADENOMA	10	15	12	5	9
#M ADENOCARCINOMA	1	1	0	2	1
#B FIBROADENOMA	10	12	16	10	16
#B CYSTADENOMA	0	0	0	0	1
#M SQUAMOUS CELL CARCINOMA	0	0	0	1	1
#M FIBROUS HISTIOCYTOMA	0	0	0	1	0
PAWS/FEET					
TOTAL NUMBER EXAMINED	5	10	8	6	3
EXAMINED, UNREMARKABLE	1	0	0	0	0
MISSING	0	1	0	1	0
TAIL					
TOTAL NUMBER EXAMINED	1	2	0	1	4

GROUP LEGEND: 1 is 0 PPM, 2 is 300 PPM, 3 is 750 PPM, 4 is 1500 PPM, 5 is 0 PPM

TABLE 18 (Continued)  
CHRONIC DIETARY TOXICITY/ONCOGENICITY STUDY WITH  
DIDECYLDIMETHYLAMMONIUMCHLORIDE IN RATS  
SUMMARY OF NEOPLASTIC MICROSCOPIC DIAGNOSES

DATA FOR ALL ANIMALS ON STUDY  
FEMALES

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	60	60	60	60	60
NUMBER OF ANIMALS	60	60	60	60	60
<b>SPLEEN</b>					
TOTAL NUMBER EXAMINED	60	9	12	59	60
EXAMINED, UNREMARKABLE	26	1	2	26	20
MISSING	0	0	0	1	0
#FIBROUS HISTIOCYTOMA	1	0	0	0	0
#HISTIOCYTIC SARCOMA	1	0	0	0	0
#HEMANGIOSARCOMA	0	0	0	0	1
#LYMPHOSARCOMA	0	0	2	1	0
<b>LYMPH NO. S-MAN</b>					
TOTAL NUMBER EXAMINED	57	16	5	60	58
EXAMINED, UNREMARKABLE	28	1	0	30	28
MISSING	3	1	0	0	2
#NEOPLASM, METASTATIC SITE	0	0	0	0	1
#HISTIOCYTIC SARCOMA	1	0	0	0	0
<b>LYMPH NO. MED</b>					
TOTAL NUMBER EXAMINED	6	9	9	6	13
MISSING	0	0	0	1	0
#NEOPLASM, METASTATIC SITE	0	0	0	0	2
<b>LYMPH NO. MES</b>					
TOTAL NUMBER EXAMINED	56	4	4	57	54
EXAMINED, UNREMARKABLE	37	0	0	21	29
TOO AUTOLYZED TO EVALUATE	0	1	0	0	0
MISSING	4	0	0	3	6
<b>LYMPH NO. REN</b>					
TOTAL NUMBER EXAMINED	0	1	1	2	1
EXAMINED, UNREMARKABLE	-	0	0	1	0
MISSING	-	1	0	0	-
<b>LYMPH NO. PANC</b>					
TOTAL NUMBER EXAMINED	2	1	0	4	1
EXAMINED, UNREMARKABLE	0	0	-	0	1
MISSING	3	0	-	0	-

GROUP LEGEND: 1 is 0 PPM, 2 is 300 PPM, 3 is 750 PPM, 4 is 1500 PPM, 5 is 0 PPM

TABLE 18 (Continued)  
CHRONIC DIETARY TOXICITY/ONCOGENICITY STUDY WITH  
DIDECYLDIMETHYLAMMONIUMCHLORIDE IN RATS  
SUMMARY OF NEOPLASTIC MICROSCOPIC DIAGNOSES

DATA FOR ALL ANIMALS ON STUDY  
FEMALES

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	60	60	60	60	60
NUMBER OF ANIMALS	60	60	60	60	60
LYMPH NO, PANC (CONTINUED)					
#M FIBROUS HISTIOCYTOMA	1	0	-	0	0
#M LYMPHOSARCOMA	0	0	-	1	0
LYMPH NO, OTHER					
TOTAL NUMBER EXAMINED	0	4	5	2	4
MISSING	1	1	1	0	2
THYMIC REGION					
TOTAL NUMBER EXAMINED	59	4	0	60	60
EXAMINED, UNREMARKABLE	54	1	-	58	57
MISSING	-	0	-	0	0
#M FIBROUS HISTIOCYTOMA	0	0	-	1	0
BONE/JOINT					
TOTAL NUMBER EXAMINED	0	1	1	0	2
#M OSTEOSARCOMA	-	0	0	-	1
BONE, STERNUM					
TOTAL NUMBER EXAMINED	59	0	0	60	60
EXAMINED, UNREMARKABLE	59	-	-	59	60
MISSING	1	-	-	0	0
BONE, FEMUR					
TOTAL NUMBER EXAMINED	60	0	0	60	60
EXAMINED, UNREMARKABLE	59	-	-	60	60
BONE, VERTEBRA					
TOTAL NUMBER EXAMINED	-	1	1	0	0
EXAMINED, UNREMARKABLE	-	1	0	-	-
BONE MARROW					
TOTAL NUMBER EXAMINED	60	0	0	60	60
EXAMINED, UNREMARKABLE	54	-	-	59	59

GROUP LEGEND: 1 is 0 PPM, 2 is 100 PPM, 3 is 750 PPM, 4 is 1500 PPM, 5 is 0 PPM

TABLE 18 (Continued)  
CHRONIC DIETARY TOXICITY/ONCOGENICITY STUDY WITH  
DIDECYLDIMETHYLAMMONIUMCHLORIDE IN RATS  
SUMMARY OF NEOPLASTIC MICROSCOPIC DIAGNOSES

DATA FOR ALL ANIMALS ON STUDY  
FEMALES

	GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP		60	60	60	60	60
NUMBER OF ANIMALS		60	60	60	60	60
BONE MARROW (CONTINUED)						
#M FIBROUS HISTIOCYTOMA		1	-	-	0	0
SKELETAL MUSCLE						
TOTAL NUMBER EXAMINED		60	60	0	60	60
EXAMINED, UNREMARKABLE		58	60	-	58	59
#M FIBROUS HISTIOCYTOMA		0	0	-	1	0
DIAPHRAGM						
TOTAL NUMBER EXAMINED		1	0	1	0	1
EXAMINED, UNREMARKABLE		0	-	1	-	1
#M HISTIOCYTIC SARCOMA		1	-	0	-	0
BRAIN						
TOTAL NUMBER EXAMINED		60	36	29	60	60
EXAMINED, UNREMARKABLE		46	15	12	56	49
#M ASTROCYTOMA		0	0	0	3	1
#M NEOPLASM, METASTATIC SITE		2	0	1	2	2
SPINAL CORD						
TOTAL NUMBER EXAMINED		59	0	0	60	59
EXAMINED, UNREMARKABLE		58	-	-	60	55
MISSING		1	-	-	0	1
NERVE, SCIATIC						
TOTAL NUMBER EXAMINED		60	0	0	60	60
EXAMINED, UNREMARKABLE		60	-	-	57	60
EYE						
TOTAL NUMBER EXAMINED		60	16	10	60	60
EXAMINED, UNREMARKABLE		52	16	8	53	55
TOO AUTOLYZED TO EVALUATE		0	1	1	0	0
HARDERIAN GL.						
TOTAL NUMBER EXAMINED		0	0	0	-	0

GROUP LEGEND: 1 is 0 PPM, 2 is 300 PPM, 3 is 750 PPM, 4 is 1500 PPM, 5 is 0 PPM

TABLE 18 (Continued)  
CHRONIC DIETARY TOXICITY/ONCOGENICITY STUDY WITH  
DIDECYLDIMETHYLAMMONIUMCHLORIDE IN RATS  
SUMMARY OF NEOPLASTIC MICROSCOPIC DIAGNOSES

DATA FOR ALL ANIMALS ON STUDY  
FEMALES

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	60	60	60	60	60
NUMBER OF ANIMALS	60	60	60	60	60
OVARIES					
TOTAL NUMBER EXAMINED	60	10	11	58	59
EXAMINED, UNREMARKABLE	43	2	3	42	41
MISSING	0	0	0	2	1
#B GRANULOSA/THECA CELL TUMOR	0	0	0	1	0
#M GRANULOSA/THECA CELL TUMOR	1	0	0	0	0
#M NEOPLASM, METASTATIC SITE	0	0	0	0	1
#M FIBROUS HISTIOCYTOMA	1	0	0	0	0
UTERUS					
TOTAL NUMBER EXAMINED	59	12	8	58	59
EXAMINED, UNREMARKABLE	43	5	3	46	43
TOO AUTOLYZED TO EVALUATE	0	0	0	1	0
MISSING	1	0	0	1	1
#B UTERINE STROMAL POLYP	3	1	7	3	0
#M UTERINE STROMAL SARCOMA	1	0	0	0	1
#B FIBROMA	1	0	0	0	0
CERVIX					
TOTAL NUMBER EXAMINED	44	3	3	36	36
EXAMINED, UNREMARKABLE	43	2	0	32	32
MISSING	16	1	0	24	24
VAGINA					
TOTAL NUMBER EXAMINED	57	0	4	59	59
EXAMINED, UNREMARKABLE	52	-	2	52	54
MISSING	3	-	0	1	1
#B STROMAL POLYP	0	-	1	0	1
#M STROMAL SARCOMA	0	-	0	0	1
LARYNX					
TOTAL NUMBER EXAMINED	0	3	0	0	0
EXAMINED, UNREMARKABLE	-	3	-	-	-
TRACHEA					
TOTAL NUMBER EXAMINED	60	3	2	60	60
EXAMINED, UNREMARKABLE	32	0	1	29	35

GROUP LEGEND: 1 is 0 PPM, 2 is 300 PPM, 3 is 750 PPM, 4 is 1500 PPM, 5 is 0 PPM

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Appendix 3

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TABLE 18 (Continued)  
CHRONIC DIETARY TOXICITY/ONCOGENICITY STUDY WITH  
DIDECYLDIMETHYLAMMONIUMCHLORIDE IN RATS  
SUMMARY OF NEOPLASTIC MICROSCOPIC DIAGNOSES

DATA FOR ALL ANIMALS ON STUDY  
FEMALES

GROUP:	1	2	3	4	5
NUMBER OF ANIMALS IN DOSE GROUP	60	60	60	60	60
NUMBER OF ANIMALS	60	60	60	60	60
LUNGS					
TOTAL NUMBER EXAMINED	60	60	60	60	60
EXAMINED, UNREMARKABLE	48	42	45	45	42
#M NEOPLASM, METASTATIC SITE	1	0	0	2	2
#M FIBROUS HISTIOCYTOMA	0	0	0	1	0
#M HISTIOCYTIC SARCOMA	1	0	0	0	0
KIDNEYS					
TOTAL NUMBER EXAMINED	60	59	60	59	59
EXAMINED, UNREMARKABLE	7	6	5	18	10
TOO AUTOLYZED TO EVALUATE	0	1	0	1	1
#M NEOPLASM, METASTATIC SITE	1	0	0	0	1
#M LYMPHOSARCOMA	0	0	0	1	0
URETER					
TOTAL NUMBER EXAMINED	1	0	0	0	2
URINARY BLADDER					
TOTAL NUMBER EXAMINED	59	3	0	56	57
EXAMINED, UNREMARKABLE	55	3	-	52	51
TOO AUTOLYZED TO EVALUATE	0	0	-	2	0
MISSING	1	0	-	2	3

GROUP LEGEND: 1 is 0 ppm, 2 is 300 ppm, 3 is 750 ppm, 4 is 1500 ppm, 5 is 0 ppm

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TABLE 19

Chronic Dietary Toxicity/Oncogenicity Study with  
Didecyldimethylammoniumchloride in Rats  
Summary of Microscopic Diagnoses

Incidence of Most Common Neoplasms

Data for all Animals on Study  
Males

NEOPLASM	Control 1	300 ppm	750 ppm	1500 ppm	Control 2	Total
Adenoma of pituitary gland	48	37	45	44	45	219
Adenoma of adrenal cortical cells	1	4	1	1	5	12
Fibroadenoma of mammary gland	0	0	0	2	0	2
Adenoma of mammary gland	1	1	1	0	0	3
Pheochromocytoma	14	8	7	6	9	44
Adenoma of pancreatic endocrine cells	1	2	3	5	8	19
Adenoma of thyroid follicular cells	3	0	2	5	1	11
Adenoma of thyroid parafollicular cells	1	1	2	0	3	7
Adenoma of testicular interstitial cells	3	1	5	7	3	19
Lipoma	3	1	2	0	0	6
Hepatocellular adenoma	3	2	4	3	3	15
Adenoma of parathyroid gland	2	0	1	1	2	6
Papilloma of skin	1	3	0	2	2	8
Fibroma	2	1	1	1	0	5
Carcinoma of pituitary	0	0	0	0	1	1
Adenocarcinoma of thyroid follicular cells	1	0	1	2	1	5
Fibrous histiocytoma	0	0	0	0	1	1
Lymphosarcoma	2	0	1	2	1	6
Undifferentiated carcinoma	0	1	0	0	1	2
Osteosarcoma	0	0	1	1	0	2
Adenoma of cutaneous basal cells	0	0	1	0	0	1
Histiocytic sarcoma	1	1	0	0	0	2
Squamous cell carcinoma	0	0	1	0	0	1
Pulmonary adenoma	1	0	0	1	0	2
Neurilemoma	1	0	0	0	0	1

NOTE: All other neoplasms had only a single occurrence in only one sex.

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TABLE 20  
Chronic Dietary Toxicity/Oncogenicity Study with  
Didecyldimethylammoniumchloride in Rats  
Summary of Microscopic Diagnoses

Incidence of Most Common Neoplasms

Data for all Animals on Study  
Females

NEOPLASM	Control 1	300 ppm	750 ppm	1500 ppm	Control 2	Total
Adenoma of pituitary gland	50	57	53	50	51	261
Adenoma of adrenal cortical cells	19	28	25	23	27	122
Fibroadenoma of mammary gland	10	12	16	10	16	64
Adenoma of mammary gland	10	15	12	5	9	51
Pheochromocytoma	2	3	3	2	0	10
Adenoma of pancreatic endocrine cells	4	0	3	3	3	13
Adenoma of thyroid follicular cells	2	1	0	4	2	9
Adenoma of thyroid parafollicular cells	6	1	0	5	4	16
Lipoma	2	1	1	1	3	8
Hepatocellular adenoma	1	1	1	4	0	7
Uterine stromal polyp	3	1	7	3	0	14
Adenoma of parathyroid gland	1	0	0	1	1	3
Fibrous Histiocytoma	2	0	0	2	1	5
Fibroma	0	0	0	2	1	3
Carcinoma of pituitary	2	0	1	1	2	6
Adenocarcinoma of thyroid follicular cells	0	0	0	1	0	1
Adenocarcinoma of mammary gland	1	1	0	2	1	5
Lymphosarcoma	0	0	2	1	0	3
Neurilemoma	0	0	0	0	1	1
Osteosarcoma	0	0	0	0	1	1
Adenocarcinoma of pancreatic exocrine cells	0	0	0	0	1	1
Vaginal stromal polyp	0	0	1	0	1	2
Adenoma of cutaneous basal cells	0	0	1	0	0	1
Cystadenoma of mammary gland	0	0	0	0	1	1
Squamous cell carcinoma	0	0	0	1	0	1
Histiocytic sarcoma	1		0	0	0	1
Carcinoma of thyroid parafollicular cells	0	0	0	0	2	2
Uterine stromal sarcoma	1	0	0	0	1	2

NOTE: All other neoplasms had only a single occurrence in only one sex.